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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,075	02/19/2004	Sean D. Monahan	Mirus.030.16.6	4417

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MIRUS CORPORATION
505 SOUTH ROSA RD
MADISON, WI 53719

EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/782,075	MONAHAN ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08/17/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-10 and 12-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-10 and 12-14* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/17/2006 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 08/17/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 04/27/2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 08/17/2006, claims 1 and 4-10 and 12-14 are pending in the application. Applicant has canceled claims 2-3 and 11.

Applicant's arguments are moot in view of the new grounds of rejections as set forth herein.

New Claim Objections and Rejections

Claim Objections

Claim 1 is objected to because is has been improperly amended. Claim 1 is currently amended to recite, "A composition ~~modified RNA~~ comprising...". The word "composition" is newly added but is not presented with the markings to indicate the changes have been made to the claim. MPEP 714 states in part "...[a]ll claims being currently amended must be presented with markings to indicate the changes that have been made relative to the immediate prior version. The changes in any amended claim must be shown by strike-through (for deleted matter) or underlining (for added matter) with 2 exceptions: (1) for deletion of five or fewer consecutive characters, double brackets may be used (e.g., [[error]]); (2) if strike-through cannot be easily perceived (e.g., deletion of number "4" or certain punctuation marks), double brackets must be used (e.g., [[4]])..."

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 recites the limitation "wherein the mammalian cell". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-6 and 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Bennett et al. (U.S. Patent No. 6,008,344).

The instant claims are drawn to a composition comprising a modified RNA and a transfection reagent wherein said modified RNA consists of a functional group post-synthetically linked to an RNA via a labile bond and wherein said functional group enhances interaction of said RNA with said transfection reagent and further wherein the function group is lined the 2'-hydroxyl ribose position, wherein the mammalian cell consist of an *in vivo* or *in vitro* mammalian cell, wherein the modified RNA is more resistant to nucleases and wherein a plurality of functional groups are attached to said RNA via labile bonds.

Bennett et al. disclose an antisense RNA molecule (see column 5, lines 44-60) wherein the RNA can be post-synthetically modified at the 2'-hydroxyl position with one or more functional groups (see column 7, lines 50-65). Bennett et al. teach compositions comprising said antisense molecules (see column 12). The specification at page 3, line 25 discloses any hydrophobic modification of RNA modification allows

hydrophobic interaction of RNA with a transfection reagent. Bennett et al. further teach chemically linking a lipid moiety such as a cholesterol moiety to the antisense RNA (see column 9, lines 13-20). Cholesterol moieties are lipid molecules that are hydrophobic, therefore, Bennett et al. teach a modified RNA comprising a cholesterol group wherein the cholesterol moiety enhances the interaction of the RNA with a transfection reagent. Bennett et al. further teach the functional group increases the RNA molecules stability and teach transfection reagents comprising said antisense RNA molecules (see columns 23 and 24). Bennett et al. specifically teach an embodiment of transfection of antisense compound in mammalian bladder carcinoma cell lines (see Example 9).

Thus, Bennett et al. anticipates claims 1, 4-6 and 12-14 of the instant application.

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-10 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bennett et al. (U.S. Patent No. 6,008,344), Tuschl et al. (cited on PTO form 892 filed 11/29/2005), Hammond et al. (Nature, 2001, Vol. 2, 110-119) and Goldsborough (cited on PTO form 892 filed 11/29/2005) and as evidenced by Letsinger et al (PNAS 1989).

The instant claims are drawn to a composition comprising a modified RNA and a transfection reagent wherein said modified RNA consists of a functional group post-synthetically linked to an RNA via a labile bond and wherein said functional group enhances interaction of said RNA with said transfection reagent and further wherein the function group is lined the 2'-hydroxyl ribose position, wherein the mammalian cell consist of an *in vivo* or *in vitro* mammalian cell, wherein the modified RNA consists of a silylated RNA, an acylated RNA, an alkylated RNA wherein the modified RNA is more resistant to nucleases and wherein a plurality of functional groups are attached to said RNA via labile bonds.

Bennett et al. disclose an antisense RNA molecule (see column 5, lines 44-60) wherein the RNA can be post-synthetically modified at the 2'-hydroxyl position with one or more functional groups (see column 7, lines 50-65). Bennett et al. teach compositions comprising said antisense molecules (see column 12). The specification at page 3, line 25 discloses any hydrophobic modification of RNA modification allows hydrophobic interaction of said RNA with a transfection reagent. Bennett et al. further teach chemically linking a lipid moiety such as a cholesterol moiety to the antisense RNA (see column 9, lines 13-20). Cholesterol moieties are lipid molecules that are hydrophobic, therefore, Bennett et al. teach a modified RNA comprising a cholesterol group wherein the cholesterol moiety enhances the interaction of the RNA with a transfection reagent. Bennett et al. further teach the functional group increases the RNA molecules stability and teach transfection reagents comprising said antisense RNA molecules (see columns 23 and 24). Bennett et al. does not teach a modified siRNA or

microRNA and does not specifically teach modified RNA consists of a silylated RNA, an acylated RNA, an alkylated RNA.

Hammond et al. teach two methods for silencing specific genes: antisense and RNA interference. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from "...questionable specificity and incomplete efficacy." (see page 110, column 1). Hammond et al. further teach "."...dsRNAs have been shown to inhibit gene expression in a sequence-specific manner" and further "RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression."

Tuschl et al. disclose a 2'-hydroxyl post-synthetically modified siRNA wherein the modification comprises a functional group attached via a bond and (see page 5 last paragraph to page 6 first paragraph) wherein the functional group increases the RNA molecules stability and would therefore enhance delivery of the RNA to the mammalian cell. Tuschl et al. siRNA comprising a plurality of functional groups attached to siRNA (see Figure 14). Tuschl et al. further disclose the modified RNA can be delivered via a transfection agent into mammalian cells *in vivo* or *in vitro* (see page 8, lines 1-18). Tuschl et al. does not teach the modified siRNA consists of a silylated RNA, an acylated RNA or an alkylated RNA.

It would have been obvious to one of ordinary skill in the art to incorporate a cholesterol moiety into a siRNA molecule.

One would have been motivated to modify a siRNA with a cholesterol moiety, as taught by Bennett et al. because Bennett et al. teach conjugating cholesterol moieties to

RNA molecules increase the nuclease affinity and intracellular uptake of said RNA. One would have been further motivated to incorporate cholesterol moieties into siRNA because both Hammond et al. and Tuschl et al. teach RNAi using siRNA is an alternative method for gene silencing that is more efficient than antisense RNA and because inhibition of gene expression is essential in elucidating gene functions, one of skill in the art would be motivated to use the most stable and gene specific inhibitor in a method of silencing gene expression. Further, one would have had a reasonable expectation of success given Bennett et al. teach chemical modifications of RNA with cholesterol were known in the art for adding stability and specificity to oligonucleotides as further evidenced by Letsinger et al. (PNAS 1989). Additionally, one would expect such modifications would benefit siRNAs because such modifications have been shown in the prior art to benefit antisense oligonucleotides.

Bennett et al., Hammond et al. or Tuschl et al. do not teach the modified siRNA consists of a silylated RNA, an acylated RNA or an alkylated RNA.

Goldsborough disclose the RNA can consist of a silylated RNA (see page 25), an acylated RNA (see page 20) or an alkylated RNA (see page 21). Goldsborough disclose the modified RNA consists of a functional group attached to a ribose 2'-hydroxyl position (see page 41), the modified RNA has more than one, but not all of the ribose 2-hydroxl positions modified (see page 13) and the modified RNA are more resistant to nucleases (see Example 61). Goldsborough disclose a modified RNA molecule comprising a functional group at the 2'-hydroxyl position (see page 21) and

wherein the functional groups increases the RNA molecule stability which would enhance delivery of the RNA to a mammalian cell.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate modification RNA such as silylated RNA, an acylated RNA or an alkylated RNA as taught by Goldsborough into the siRNA as taught by Tuschl et al.

One would have been motivated to incorporate modified silylated RNA, acylated RNA or alkylated RNA into siRNA because Goldsborough teach incorporating silylated RNA, acylated RNA or an alkylated RNA into a RNA molecule protects the RNA from degradation. Goldsborough teach RNA is inherently unstable and protecting RNA from degradation while maintaining the biological activity of RNA is essential for use by one of skill in the art (see pages 3-4). Goldsborough et al. teach modification of gene expression inhibitors such as an antisense molecule would have enhanced activity compared to natural nucleic acid molecules because they are more stable and able to enter the cell more readily (see page 71). As such, one would be motivated to increase the stability of a siRNA molecule to increase the potential for greater RNAi activity or prolonged activity of the siRNA molecule in a cell.

Finally, one would have a reasonable expectation of success because Goldsborough teach successful incorporation of a silylated RNA, acylated RNA or an alkylated RNA into a RNA molecule and further teach incorporation of such RNA does not affect the biological activity of the modified RNA.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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Kimberly Chong
Examiner
Art Unit 1635

SEAN McGARRY
PRIMARY EXAMINER
1635